

Sphingosine-1-phosphate enhances satellite cell activation in dystrophic muscles through a S1PR2/STAT3 signaling pathway.

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Public Summary:

Sphingosine-1-phosphate (S1P) activates a widely expressed family of G protein-coupled receptors, serves as a muscle growth factor and activates muscle stem cells called satellite cells. Here we show that muscle injury induces dynamic changes in S1P signaling and metabolism in vivo, and that S1P biosynthesis is required to support efficient muscle regeneration and satellite cell proliferation and differentiation. Mdx mice, a model for muscular dystrophy, were found to be S1P-deficient and to exhibit up-regulation of SPL, an enzyme that breaks down S1P. Pharmacological SPL inhibition increased muscle S1P levels, improved mdx muscle regeneration and enhanced satellite cell proliferation. Our findings suggest that S1P promotes satellite cell progression through the cell cycle, and that SPL inhibition may provide a therapeutic strategy for muscular dystrophy.

Scientific Abstract:

Sphingosine-1-phosphate (S1P) activates a widely expressed family of G protein-coupled receptors, serves as a muscle trophic factor and activates muscle stem cells called satellite cells (SCs) through unknown mechanisms. Here we show that muscle injury induces dynamic changes in S1P signaling and metabolism in vivo. These changes include early and profound induction of the gene encoding the S1P biosynthetic enzyme SphK1, followed by induction of the catabolic enzyme sphingosine phosphate lyase (SPL) 3 days later. These changes correlate with a transient increase in circulating S1P levels after muscle injury. We show a specific requirement for SphK1 to support efficient muscle regeneration and SC proliferation and differentiation. Mdx mice, which serve as a model for muscular dystrophy (MD), were found to be S1P-deficient and exhibited muscle SPL upregulation, suggesting that S1P catabolism is enhanced in dystrophic muscle. Pharmacological SPL inhibition increased muscle S1P levels, improved mdx muscle regeneration and enhanced SC proliferation via S1P receptor 2 (S1PR2)-dependent inhibition of Rac1, thereby activating Signal Transducer and Activator of Transcription 3 (STAT3), a central player in inflammatory signaling. STAT3 activation resulted in p21 and p27 downregulation in a S1PR2-dependent fashion in myoblasts. Our findings suggest that S1P promotes SC progression through the cell cycle by repression of cell cycle inhibitors via S1PR2/STAT3-dependent signaling and that SPL inhibition may provide a therapeutic strategy for MD.

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